The Effect of Vitamin C on Clinical Outcome in Critically Ill Patients: A Systematic Review With Meta-Analysis of Randomized Controlled Trials

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Abstract: OBJECTIVES The effects of vitamin C administration on clinical outcome in critically ill patients remain controversial. DATA SOURCES Online databases were searched up to October 1, 2018. STUDY SELECTION We included randomized controlled trials on the use of vitamin C (any regimen) in adult critically ill patients versus placebo or no therapy. DATA EXTRACTION Risk ratio for dichotomous outcome and standardized mean difference for continuous outcome with 95% CI were calculated using random-effects model meta-analysis. DATA SYNTHESIS Forty-four randomized studies, 16 performed in ICU setting (2,857 patients) and 28 in cardiac surgery (3,598 patients), published between 1995 and 2018, were included in the analysis. In ICU patients, vitamin C administration was not associated with a difference in mortality (risk ratio, 0.90; 95% CI, 0.74-1.10; p = 0.31), acute kidney injury, ICU or hospital length of stay compared with control. In cardiac surgery, vitamin C was associated to a reduction in postoperative atrial fibrillation (risk ratio, 0.64; 95% CI, 0.52-0.78; p < 0.0001), ICU stay (standardized mean difference, -0.28 d; 95% CI, -0.43 to -0.13 d; p = 0.0003), and hospital stay (standardized mean difference, -0.30 d; 95% CI, -0.49 to -0.10 d; p = 0.002). Furthermore, no differences in postoperative mortality, acute kidney injury, stroke, and ventricular arrhythmia were found. CONCLUSIONS In a mixed population of ICU patients, vitamin C administration is associated with no significant effect on survival, length of ICU or hospital stay. In cardiac surgery, beneficial effects on postoperative atrial fibrillation, ICU or hospital length of stay remain unclear. However, the quality and quantity of evidence is still insufficient to draw firm conclusions, not supporting neither discouraging the systematic administration of vitamin C in these populations. Vitamin C remains an attractive intervention for future investigations aimed to improve clinical outcome.

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Objectives: The effects of vitamin C administration on clinical outcome in critically ill patients remain controversial.

Data Sources: Online databases were searched up to October 1, 2018.

Study Selection: We included randomized controlled trials on the use of vitamin C (any regimen) in adult critically ill patients versus placebo or no therapy.

Data Extraction: Risk ratio for dichotomous outcome and standardized mean difference for continuous outcome with 95% CI were calculated using random-effects model meta-analysis.

Data Synthesis: Forty-four randomized studies, 16 performed in ICU setting (2,857 patients) and 28 in cardiac surgery (3,598 patients), published between 1995 and 2018, were included in the analysis. In ICU patients, vitamin C administration was not associated with a difference in mortality (risk ratio, 0.90; 95% CI, 0.74–1.10; $p = 0.31$), acute kidney injury, ICU or hospital length of stay compared with control. In cardiac surgery, vitamin C was associated to a reduction in postoperative atrial fibrillation (risk ratio, 0.64; 95% CI, 0.52–0.78; $p < 0.0001$), ICU stay (standardized mean difference, −0.28 d; 95% CI, −0.43 to −0.13 d; $p = 0.0003$), and hospital stay (standardized mean difference, −0.30 d; 95% CI, −0.49 to −0.10 d; $p = 0.002$). Furthermore, no differences in postoperative mortality, acute kidney injury, stroke, and ventricular arrhythmia were found.

Conclusions: In a mixed population of ICU patients, vitamin C administration is associated with no significant effect on survival, length of ICU or hospital stay. In cardiac surgery, beneficial effects on postoperative atrial fibrillation, ICU or hospital length of stay remain unclear. However, the quality and quantity of evidence is still insufficient to draw firm conclusions, not supporting neither discouraging the systematic administration of vitamin C in these populations. Vitamin C remains an attractive intervention for future investigations aimed to improve clinical outcome. (*Crit Care Med* 2019; XX:00–00)

Key Words: ascorbic acid; cardiac surgery; critical care; intensive care; perioperative medicine; vitamin C

Most critically ill patients, such as those with septic shock or undergoing cardiac surgery, suffer from pathophysiologic conditions that lead toward a systemic inflammatory response that can increase oxidative stress. In this scenario, there is a drastic reduction in plasma levels of various micronutrients and trace elements with antioxidant properties, whereas the circulating oxidative molecules rise, resulting in an overwhelming increase of their levels that can lead to organ failure and death (1–4). Therefore antioxidant defenses repletion could theoretically results in a beneficial therapeutic effect in the critically ill patient (4). However, randomized evidence on antioxidant is highly inconsistent, with no clear benefit yet established.

Vitamin C, also known as ascorbic acid or ascorbate, is an antioxidant molecule with pleiotropic properties that may contribute to reduce oxidative stress and organ dysfunction, together with a positive impact on tissue perfusion (2). It has been suggested that vitamin C may be helpful as adjunctive therapy in septic shock (5) and it may also play a role in cardiac surgery, particularly in prevention of postoperative atrial fibrillation (6). Furthermore, IV vitamin C administration could be an effective way to restore the physiologic levels of

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this micronutrient, and supra-physiologic doses of vitamin C could have further beneficial effects (7–9). Side effects are rare, but reported in the literature (1, 4, 10). Nevertheless, despite there is a rationale in favor of the use of vitamin C, the clinical effectiveness of vitamin C supplementation is still unclear. In this systematic review with meta-analysis, meta-regression, and trial sequential analysis (TSA), we aimed to assess the effect of vitamin C administration on major clinical outcome in ICU or cardiac surgery patients.

MATERIALS AND METHODS

The present systematic review was conducted in compliance with Cochrane methodology (11), Preferred Reporting Items Systematic Reviews and Meta-Analysis (PRISMA) guidelines (12), and according to a pre-published protocol on the international prospective register of systematic reviews (PROSPERO, CRD42017069790). A complete PRISMA checklist is provided in **eTable 1** (Supplemental Digital Content 1, http://links.lww.com/CCM/E416) (13).

Search Strategy

Two investigators (A.P.,V.F.G.) independently searched PubMed, EMBASE, and the Cochrane Central Register of clinical trials (last updated October 1, 2018) for appropriate articles. The full PubMed search strategy is available in the supplement (**eMethods 1**, Supplemental Digital Content 1, http://links.lww.com/CCM/E416) and it includes all the most common vitamin C definitions employed in the literature. Abstracts from recent international conferences were searched for additional relevant studies. In addition, we hand scanned references of retrieved articles and pertinent reviews of the literature. No language restriction was enforced.

Study Selection

References obtained from searches were first independently examined at an abstract level by two investigators (A.P., V.F.G) and then, if potentially relevant, collected as complete articles. Eligible studies met the following PICOS criteria: 1) Population: adult ICU or cardiac surgery patients; 2) Intervention: any type of vitamin C formulation and regimen; 3) Comparison intervention: placebo or no therapy; 4) Outcome: mortality at longest follow-up available; and 5) Study design: randomized controlled trials (RCTs). There were no restrictions on vitamin C formulation and dose or time of administration. The exclusion criteria were overlapping populations and pediatric studies. Two investigators (A.P., A.M.D.) independently assessed selected studies for the final analysis, with eventual divergences finally resolved by consensus. If the article did not report data on primary or secondary outcomes, the corresponding author was contacted for further information.

Data Abstraction and Study Characteristics

Three authors (A.P., A.M.D., V.F.G.) extracted relevant information from each selected study and entered them into predefined databases; divergences were resolved by consensus with a fourth author (G.L.). We collected potential sources of significant clinical heterogeneity, such as study design, sample size, clinical setting, inclusion and exclusion criteria, vitamin C regimen and association with other drugs, control treatment, as well as primary and secondary endpoints. We evaluated the possible authors' conflicts of interests and the funding of each study.

The primary endpoint of the present review was mortality at the longest follow-up available. Secondary outcomes included acute kidney injury (AKI), supraventricular arrhythmia, ventricular arrhythmia, stroke, length of ICU stay, and length of hospital stay. The outcomes were reported as per-trial definition. We applied the intention-to-treat methods whenever possible.

Internal Validity and Risk of Bias Assessment

The internal validity of each trial included was independently evaluated by two authors (A.P., A.M.D.) for bias according to The Cochrane Collaboration methods (11) (**eMethods 2**, Supplemental Digital Content 1, http://links.lww.com/CCM/E416). Eventual divergences were resolved by consensus. We rated the potential risk of bias by applying a rating of "low," "high," or "unclear" to each study.

Data Analysis and Synthesis

For dichotomous variables, we calculated the odds ratio (OR) with a 95% CI and in case of common events, defined as the frequency of the event occurring in the control group more than or equal to 10%, we calculated the risk ratio (RR) with a 95% CI. For continuous outcome, we calculated standardized mean difference (sMD) with 95% CI. The p value for the comparison between the groups was calculated, and a p value of less than or equal to 0.05 was considered as statistically significant. Heterogeneity was assessed using the chi-square test and the I^2 statistic. We post hoc decided to include only ICU and cardiac surgery patients, presenting the results separately using a random-effects model meta-analysis. Publication bias was assessed by visually inspecting funnel plots if 10 or more trials are included in the meta-analysis (11). We performed various sensitivity, subgroup, and meta-regression analyses (**eMethods 3**, Supplemental Digital Content 1, http://links.lww.com/CCM/E416). Meta-analysis was performed using Review Manager (RevMan, Version 5.3. Copenhagen, Denmark: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

TSA is a methodology that could quantify the statistical reliability of data in a cumulative meta-analysis adjusting significance levels for the risks of random errors due sparse data and repetitive testing on accumulating data. The TSA combines an information size calculation (equal to the cumulated sample sizes of all included trials), with a threshold for a statistically significant effect and a threshold for futility of the intervention, both adjusted to better control of type I and type II errors. Conclusions made using TSA show the potential to be more consistent than those using traditional meta-analysis methodology (14–16). Therefore, we performed a post hoc random-effects TSA for mortality with the intent of maintaining an overall 5% risk of type I error and a 10% risk of type II error, at a power of 90% (14–16). We assumed a relative risk

reduction of 15%, and we derived the control event proportion from the actual control dataset. The resulting required information size was further diversity (D2)-adjusted. We used the TSA software (TSA Viewer [Computer program], Version 0.9.5.5 Beta, Copenhagen Trial Unit, Centre for Clinical Intervention Research, Rigshospitalet, Copenhagen, Denmark, 2016).

RESULTS

The selection process is summarized in **Figure 1**. A total of 1,894 studies were identified and, after exclusion of ineligible studies, 44 studies ($n = 6,455$) were included in the meta-analysis (8–10, 17–61). Major exclusions are reported in **eTable 2** (Supplemental Digital Content 1, http://links.lww.com/CCM/E416).

Thirty-four studies were single-center, one trial was two-centers, three trials were three-centers, and one trial was multicenter. In 10 cases, we received further information from the authors (21, 23, 31, 38, 39, 50, 53, 60–62) (**eTable 3**, Supplemental Digital Content 1, http://links.lww.com/CCM/E416).

Three trials were considered to carry a low risk of bias in all bias domains (20, 45, 58), five trials were at unclear risk of bias (9, 22–24, 40), and 36 trials were at high risk of bias (**eFigs. 1** and **2**, Supplemental Digital Content 1, http://links.lww.com/CCM/E416).

ICU Patients

Sixteen studies (2,857 patients) administered vitamin C supplements in critically ill ICU patients: six in a general ICU population (2,425 patients), six in a septic population (260 patients), three in patients with severe acute pancreatitis (135 patients), and one in patients with major burns (37 patients) (**Table 1**; and **eTable 4**, Supplemental Digital Content 1, http://links.lww.com/CCM/E416).

The administration of vitamin C in critically ill patients was associated with no difference in mortality at the longest follow-up available (400 of 1,453 patients [28%] in the vitamin C group vs 411 of 1,404 [29%] in the control group; RR, 0.90; 95% CI, 0.74–1.10; $p = 0.31$) (**Fig. 2**). Funnel plot was symmetric, not suggesting publication bias (**eFig. 3**, Supplemental Digital Content 1, http://links.lww.com/CCM/E416). Similar results were found at subgroup analyses, in particular when assessing trials giving only vitamin C, IV/enteral vitamin C, and high-dose IV vitamin C (**Fig. 3**; and **eTable 5**, Supplemental Digital Content 1, http://links.lww.com/CCM/E416).

TSA was inconclusive, since 19.40% of the information size was accrued and the cumulative curve did not reach the area of futility (**Fig. 4**), suggesting the need of further trials for a firm conclusion on the effects of vitamin C therapy.

Vitamin C administration was associated with no significant reduction in length of ICU stay in critically ill patients (**eFig. 4**, Supplemental Digital Content 1, http://links.lww.com/CCM/E416).

No significant difference in AKI between vitamin C and control was found (RR, 1.03; 95% CI, 0.84–1.25; $p = 0.78$; TSA inconclusive) and in

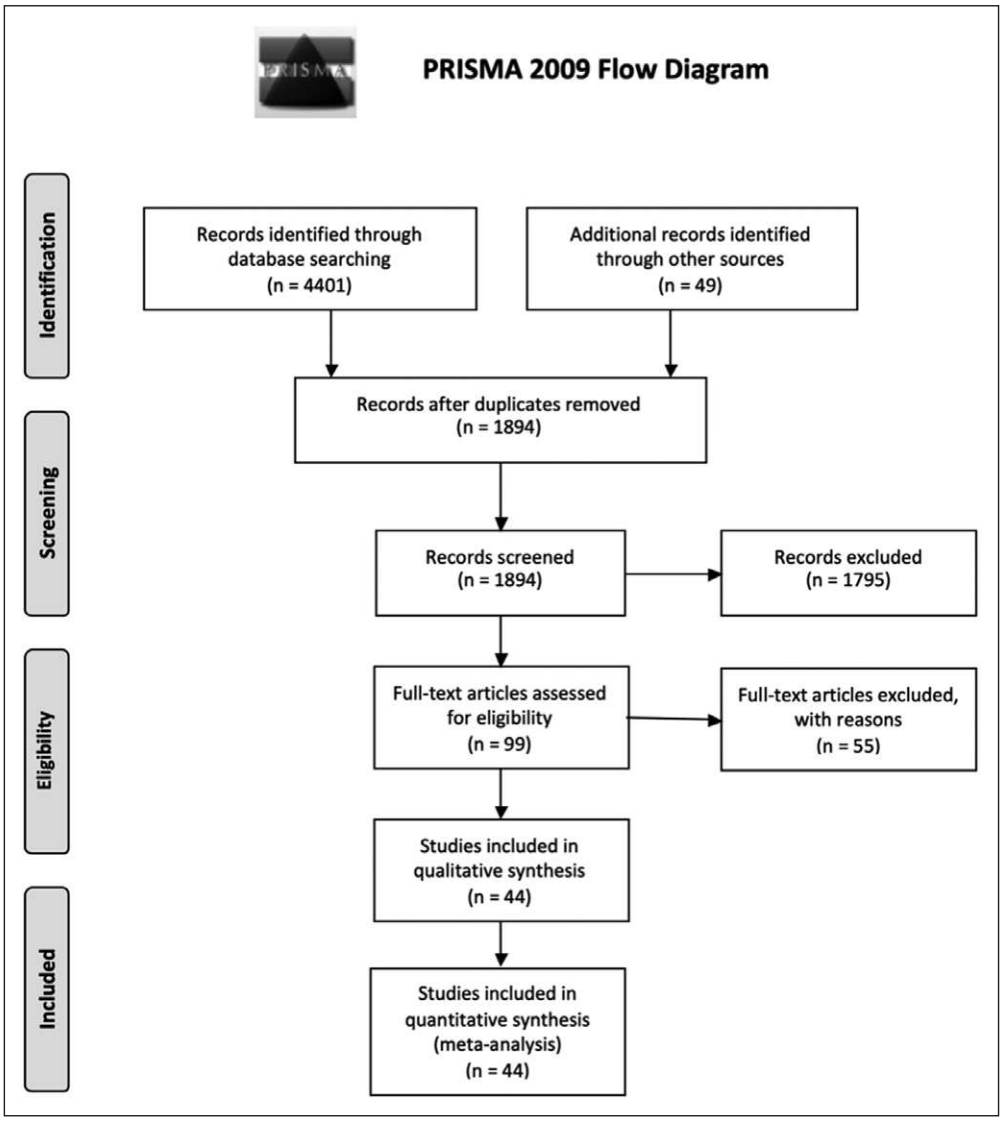

Figure 1. Study flow diagram. PRISMA = Preferred Reporting Items Systematic Reviews and Meta-Analysis.

TABLE 1. Characteristics of the ICU Trials Included in the Analysis

References	Journal	Country	Setting	No. of Patients	Experimental Intervention	Vitamin C Regimen	Control
ICU patients							
Bansal et al (19)	*Saudi J Gastroenterol*	India	Acute pancreatitis	39	Vitamin C, vitamin E, vitamin A	Vitamin C 1,000 mg IV qd for 14 d	No treatment
Berger et al (20)	*Crit Care*	Switzerland	Mixed ICU	200	Vitamin C, vitamin B1, selenium, zinc	Vitamin C 1,100 mg IV bid on first 2 d and qd until day 5	Placebo
Crimi et al (24)	*Anesth Analg*	Italy	Mixed ICU	216	Vitamin C, vitamin E	Vitamin C 500 mg E qd for 10 d	Placebo
Ferrón-Celma et al (30)	*J Surg Res*	Spain	Sepsis/septic shock	20	Vitamin C	Vitamin C 450 mg IV qd for 6 d	Placebo
Fowler et al (7)	*J Transl Med*	United States	Sepsis/septic shock	24	Vitamin C	Vitamin C 12.5 or 50 mg/kg IV qid for 4 d	Placebo
Galley et al (31)	*Free Radic Biol Med*	United Kingdom	Sepsis/septic shock	30	Vitamin C, vitamin E, NAC	Vitamin C 1,000 mg IV qd for 1 d	Placebo
Heyland et al (58)	*N Engl J Med*	United States, Canada, Europe	Mixed ICU	1,218	Vitamin C, vitamin E, zinc, beta-carotene, selenium, ± glutamine	Vitamin C 1,500 mg E qd for 28 d or until ICU discharge	Placebo
Howe et al (9)	*Am J Crit Care*	United States	Mixed ICU	72	Vitamin C, vitamin E, ± NAC	Vitamin C 1,000 mg E qd for 28 d or until ICU discharge	Placebo
Nabil Habib et al (54)	*Int J Microbiol Adv Immunol*	Egypt	Sepsis/septic shock	100	Vitamin C	Vitamin C 1,500 mg IV qid until ICU discharge	No treatment
Nathens et al (8)	*Ann Surg*	United States	Mixed ICU	595	Vitamin C, vitamin E	Vitamin C 1,000 mg IV three times a day until ICU discharge	No treatment
Palli et al (33)	*Crit Care*	Greece	Mixed ICU	124	Vitamin C, NAC	Vitamin C 2,000 mg IV 2 hr before and at 10 hr and 18 hr following the infusion of contrast agent	Placebo
Sateesh et al (44)	*Trop Gastroenterol*	India	Acute pancreatitis	53	Vitamin C, NAC, multivitaminic compound	Vitamin C 500 mg E qd for 5 d	No treatment
Schneider et al (55)	*Clin Nutr*	Germany	Sepsis/septic shock	58	Vitamin C, vitamin E, glutamine, beta-carotene, selenium, zinc, glycine, tributyrin	Vitamin C 1,500 mg E qd	Placebo
Siriwardena et al (45)	*Gut*	United Kingdom	Acute pancreatitis	43	Vitamin C, NAC, selenium	Vitamin C 2,000 mg IV over 24 hr for the first 2 d and 1,000 mg IV over 24 hr for the following 5 d	Placebo
Tanaka et al (47)	*Arch Surg*	Japan	Burn patients	37	Vitamin C	Vitamin C 66 mg/kg/hr IV for 24 hr	No treatment
Zabet et al (49)	*J Res Pharm Pract*	Iran	Sepsis/septic shock	28	Vitamin C	Vitamin C 25 mg/kg enteral qid for 3 d	Placebo

E = enteral, NAC = N-acetylcysteine, qd = once a day, qid = four times a day.

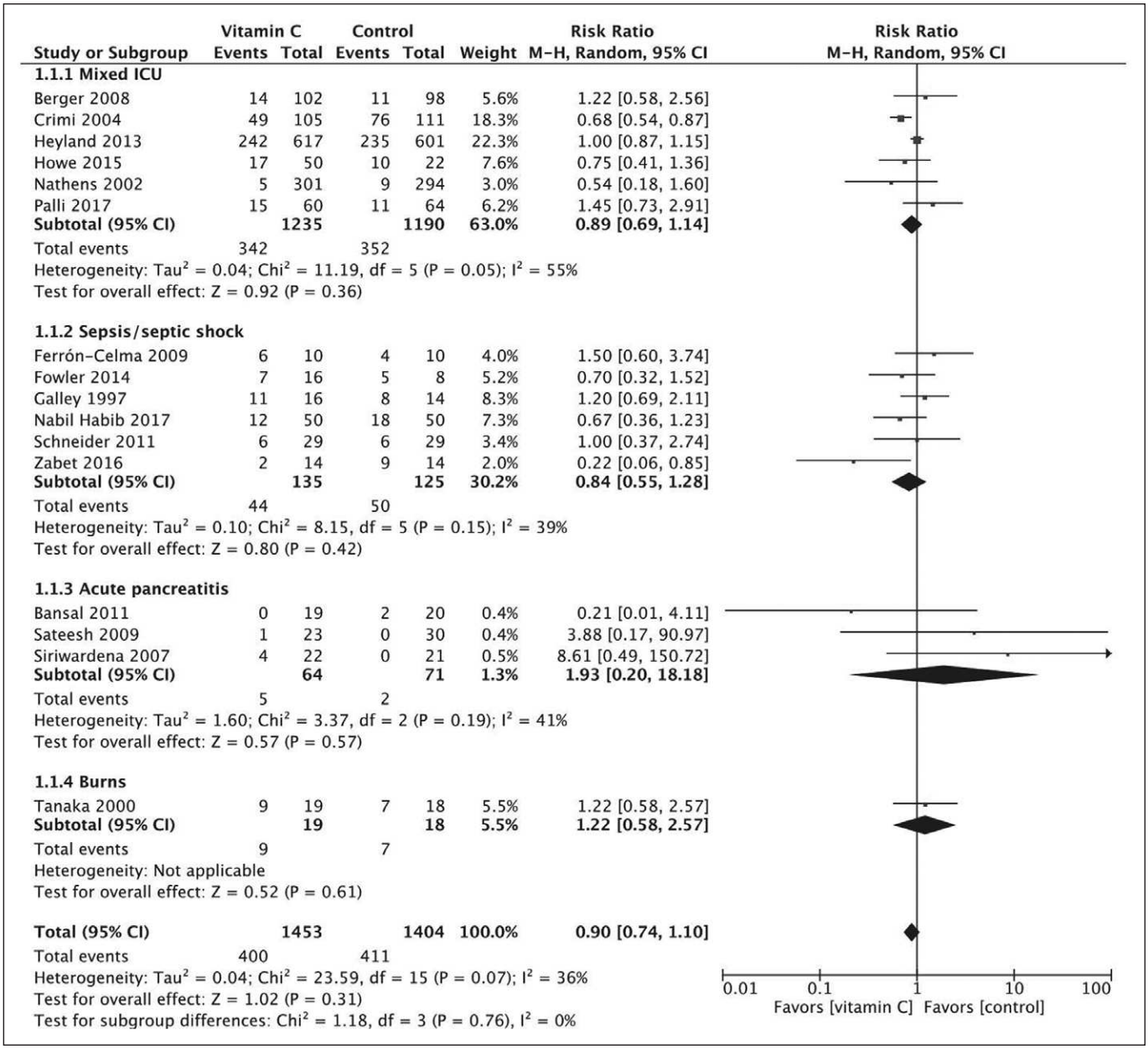

Figure 2. Mortality in ICU patients. Forest plot for mortality at longest follow-up available in patients randomized to vitamin C (any regimen) or control. *df* = degrees of freedom, M-H = Mantel-Haenszel.

other secondary outcomes (**eFig. 5** and **eTable 4**, Supplemental Digital Content 1, http://links.lww.com/CCM/E416).

Cardiac Surgery

Twenty-eight trials administered vitamin C supplements in cardiac surgery (3,598 patients): 21 in coronary artery bypass grafting surgery (2,465 patients) and seven in a mixed cardiac surgery population (1,133 patients) (**eTables 6** and **7**, Supplemental Digital Content 1, http://links.lww.com/CCM/E416).

Mortality rate was low and similar between vitamin C and control group (15 of 968 patients [1.55%] in the vitamin C group vs 17 of 927 [1.83%] in the control group; RR, 1.00; 95% CI, 0.48–2.08; $p = 1.00$; TSA inconclusive) (**eFig. 6**, Supplemental Digital Content 1, http://links.lww.com/CCM/E416).

Vitamin C was associated with lower supraventricular arrhythmias versus control in cardiac surgery patients (RR, 0.64; 95% CI, 0.52–0.78; $p < 0.0001$). Atrial fibrillation was the main reported supraventricular arrhythmia. The analysis was limited by the high statistical heterogeneity ($I^2 = 57\%$; $p_{\text{heterogeneity}} = 0.0005$) and significant asymmetry of funnel plot, suggesting publication bias; most of the heterogeneity was explained by Europe/United States trials, which found no difference in postoperative supraventricular arrhythmias (RR, 0.92; 95% CI, 0.76–1.11; $p = 0.38$) in comparison to an important significant effect in other countries (RR, 0.49; 95% CI, 0.39–0.61; $p < 0.00001$)

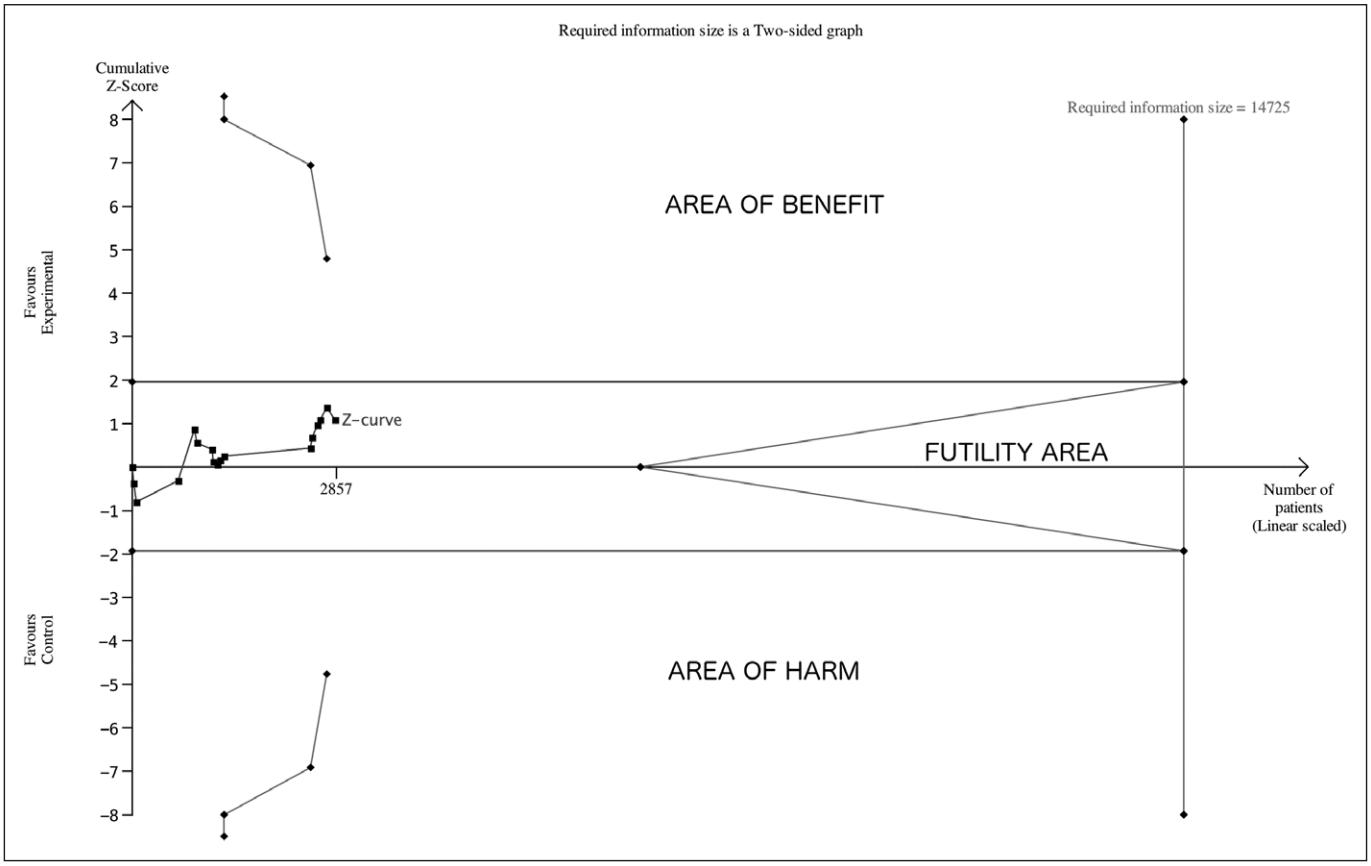

Figure 3. Trial sequential analysis for mortality at longest follow-up available in a mixed ICU population. Trial sequential analysis of the included trials (*black square fill icons*) shows that the cumulative *Z* curve did not cross nor the traditional boundary nor the trial sequential monitoring boundary for futility and did not reach the required information size ($n = 14{,}725$), suggesting the need for more trials to establish firm conclusions about vitamin C effects in critically ill patients. *X*-axis: the number of patients randomized; *y*-axis: the cumulative *z* score; *horizontal dotted lines*: conventional boundaries (upper for benefit, *z* score = 1.96, lower for harm, *z* score = −1.96, two-sided, $p = 0.05$); *oblique lines* with *diamond icons*: trial sequential monitoring boundaries; *oblique line* with *square fill icons*: *Z* curve; and *vertical line* with *diamonds*: required information size.

($p_{subgroup} < 0.0001$) (**eFigs. 7** and **8**, Supplemental Digital Content 1, http://links.lww.com/CCM/E416).

Vitamin C administration was associated to a small reduction in postoperative length of ICU stay (sMD, –0.28 d; 95% CI, –0.43 to –0.13 d; $p = 0.0003$) and hospital stay (sMD, –0.30 d; 95% CI, –0.49 to –0.10 d; $p = 0.002$). The results were limited by high statistical heterogeneity ($I^2 > 62\%$; $p_{heterogeneity} < 0.001$) and possible publication bias. Subgroup analysis including only Europe/United States trials found no effects of vitamin C on length of ICU or hospital stay (**eFigs. 9-11** and **eTable 8**, Supplemental Digital Content 1, http://links.lww.com/CCM/E416).

No significant differences in ventricular arrhythmia (OR, 0.79; 95% CI, 0.33–1.88; $p = 0.59$; TSA inconclusive), AKI (RR, 1.18; 95% CI, 0.74–1.89; $p = 0.48$; TSA inconclusive), and stroke (OR, 0.47; 95% CI, 0.13–1.69; $p = 0.25$; TSA inconclusive) were found (eFig. 6, Supplemental Digital Content 1, http://links.lww.com/CCM/E416).

Vitamin C Regimens

The results were consistent at subgroup, sensitivity, and meta-regression analyses. No effects of dose, length of therapy, route of administration, and combination with other antioxidants were suggested on any outcome assessed in ICU patients. In cardiac surgery, meta-regression suggested possible beneficial effects of longer supplementation with low-dose vitamin C on supraventricular arrhythmia (**eTables** 5, **8** and **9**, and **eMethods** 1, Supplemental Digital Content 1, http://links.lww.com/CCM/E416).

DISCUSSION

This meta-analysis of RCTs showed that vitamin C supplementation, alone or in association with other antioxidant drugs, is associated with no effects on survival and ICU or hospital stay in a mixed population of ICU patients. In cardiac surgery, the observed beneficial effects on postoperative atrial fibrillation and ICU/hospital length of stay remain unclear, due to the presence of publication bias and subgroup effects according to geographical area. The quality and quantity of randomized evidence is still insufficient to draw firm conclusions on clinical effects of vitamin C, not supporting neither discouraging the systematic administration in critically ill patients.

Cardiac surgery and ICU patients represent two different populations, often managed by same medical teams. Oxidative stress plays a central role in the pathophysiology of

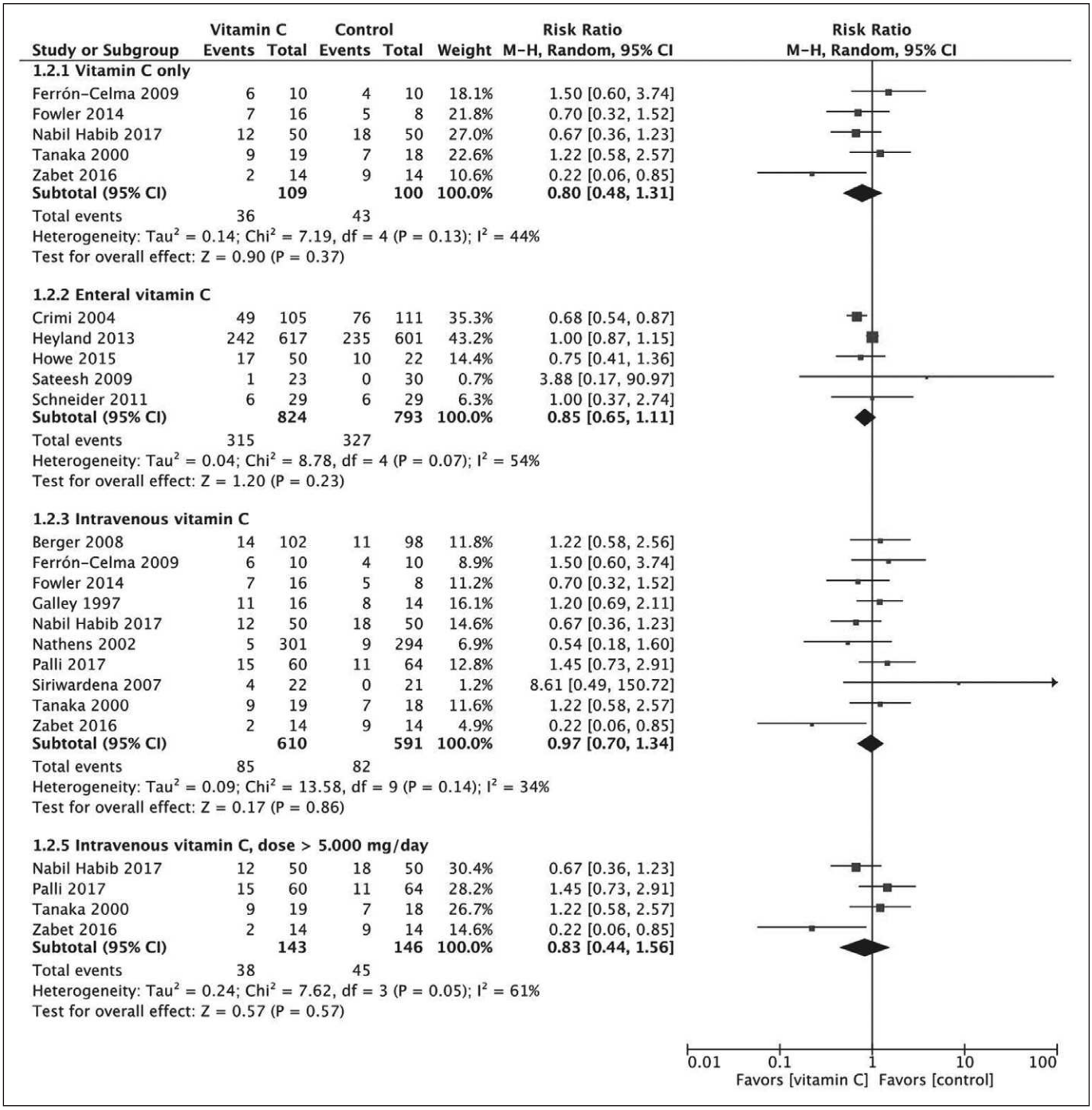

Figure 4. Main subgroup analyses in a mixed ICU population. Forest plot for mortality at longest follow-up available in patients randomized to receive: only vitamin C, enteral vitamin C (any regimen), IV vitamin C (any regimen), or high-dose IV vitamin C (> 5,000 mg a day). *df* = degrees of freedom, M-H = Mantel-Haenszel.

inflammatory syndrome in both populations. A high proportion of surgical ICU patients suffer from vitamin C deficiency (60) and, in addition, the intense inflammatory response can increase metabolic turnover of vitamin C resulting in a severe deficiency (61). Analogously, the use of cardiopulmonary bypass in cardiac surgery can also induce oxidative stress leading to vitamin C depletion (62). An imbalance in the production of oxidizing species, such as reactive oxygen species, superoxide anions, and other radicals, leads to an increased oxidative stress, which causes an increased endothelial permeability with an impairment of microcirculatory flow, an inadequate cell-mediated immunity, followed by an activation of apoptotic mitochondrial mechanisms that may contribute to cell death and organ failure (4, 5). Hypothetically, vitamin C can counterbalance oxidizing species, providing a preventing role in the oxidative stress development and restoring neutrophil function (4, 5). Some randomized trials included in the present meta-analysis have shown an improvement in the inflammatory profile of ICU patients

receiving vitamin C, confirming its potential immunomodulatory activity (7, 8, 24). Indeed, two of these studies showed also an improvement in organ dysfunction and failure (7, 8), as also suggested by a recent nonrandomized trial (63). Despite vitamin C might exert various positive effects, our analysis failed to find any benefit in terms of mortality.

Human cells have vitamin C transporters coupled with sodium transport and their activity is limited by blood level of vitamin C; kidneys excrete the excess of vitamin C and its blood levels remain strictly controlled (64). Thus, higher doses of vitamin C administered orally (> 400 mg) can saturate the intestinal absorption system, achieving plasma concentrations that may not be enough to scavenge an excess of oxidizing species (64, 65). In this scenario, IV infusion route should be the preferred in order to achieve higher plasma concentrations in order to scavenge oxidizing species, protecting from their undesirable effects (66). For this purpose, doses higher than the usually recommended daily intake could be recommended especially if we consider that, given the hydrophilic chemical structure of vitamin C, its plasma concentrations may be affected by the higher distribution volume due to the positive fluid balance that critically ill patients frequently suffer from (67). A dosage of 2–3 g per day might be needed to restore normal levels of vitamin C in critically ill patients (68). However, our study failed to find any subgroup effects in patients randomized to receive IV or high-dose ascorbic acid.

Higher levels of oxidizing species can cause tubular injury and glomerular edema, leading to AKI (69). Recent findings from a retrospective before-after study suggest that the early use of IV vitamin C, together with corticosteroids and thiamine, may be effective in preventing progressive organ dysfunction including AKI and reducing the mortality of septic shock (63). However, the external validity of this retrospective study is limited, mainly due to the nonrandomized, single-centered design, the small sample size, and the presence of baseline imbalances and other limitations (70). Our analysis did not show any effect in terms of renal failure, even if AKI can be a rare complication of vitamin C therapy and represents so an outcome of interest, it was underreported in the included trials. Results from cardiac surgery, another setting where AKI prevention is crucial, were inconclusive too.

In cardiac surgery, vitamin C administration has emerged as a strategy of postoperative atrial fibrillation prevention (6). The substantial difference in atrial fibrillation results from Europe/United States in comparison to other countries, together with substantial publication bias (6, 71), rise doubts on the external validity of the positive aggregate results of our meta-analysis on atrial fibrillation in cardiac surgery. Some epidemiologic evidence suggested possible larger treatment effects in less developed countries (72). Nevertheless, differences in population characteristics, lifestyle factors including nutrition, treatment response, and healthcare systems exist and, at least partially, could explain the large difference in effect estimate. The prevention of atrial fibrillation, a potential source of embolic stroke, together with the evidence that oxidizing species enhance secondary brain damage by means of increased permeability of blood-brain barrier generating edema in the acute stage of stroke (73, 74), leave a role for vitamin C. Once again, our results do not firmly support this hypothesis.

This is the first comprehensive meta-analysis systematically assessing the effects of vitamin C supplementation on important clinical outcomes in critically ill patients. With 44 trials and more than 6,000 patients, this is the largest meta-analysis on this topic performed to date. We focused on some important clinical outcomes, such as mortality, and we performed a systematic review of several databases, aiming to reduce the possibility of missing minor publications. Traditional limitations of aggregate patient data meta-analyses are present, including different patients baseline characteristics, clinical subsettings, and different vitamin C regimens. In particular, differences in routes of administration (enteral vs IV), dosage (low- vs high-dose), total duration of supplementation, and combined treatment with other antioxidants drugs, increase the inconsistency of the aggregate analysis. However, we performed several subgroup analyses to explore the possible effects of different vitamin C regimens, with inconclusive results. Most of the eligible trials had an high risk of bias and publication bias is probable (6). In ICU trials, mortality and length of ICU or hospital stay were the most reported outcomes and several other outcomes of interests, such as organ failure or quality-of-life endpoints, were modestly and heterogeneously reported. On the contrary, atrial fibrillation was the most reported outcome in cardiac surgery while mortality was low, making the aggregate analysis underpowered for this latter outcome.

Adverse effects following vitamin C administration are limited (1, 4) and are mainly related to oxalate kidney stones formation and oxalate nephropathy (10). However, most of the included trials did not systematically assess adverse effects, and a systematic evaluation before extensive implementation of vitamin C therapy is warranted.

These issues, together with inconclusive results from TSA, suggest that the actual randomized evidence on vitamin C supplementation is inconsistent and the current use of vitamin C as adjunctive therapy cannot be recommended or discouraged neither in a mixed population of ICU patients nor in cardiac surgery.

CONCLUSIONS

Vitamin C administration is not associated with a reduction in mortality in a mixed ICU population. In cardiac surgery, the observed beneficial effects on postoperative atrial fibrillation and ICU/hospital length of stay remain unclear, due to the presence of publication bias and subgroup effects according to geographical area. The quality and quantity of evidence is still insufficient to draw firm conclusions on the possible effect of vitamin C on clinical outcome and aggregate randomized evidence does not support neither discourage the systematic administration of vitamin C in ICU or cardiac surgery. Vitamin C remains an attractive intervention for future investigations aimed at reducing mortality and morbidity.

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